

*Anderson et al.*  
*Serial No.: 09/921,004*  
*Page 7 of 12*

**REMARKS/ARGUMENTS**

In response to the Rejection mailed December 16, 2003, Applicants have newly canceled claims 26, 28 and 36, newly amended claims 1, 3, 4, 5, 7, 27, 30-35 and 38, added new claims 39-41 and present the following remarks.

Claims 1, 3-39 and 25-38 were rejected under 35 USC 112, first paragraph, as not being described in the specification. Specifically, the examiner contends that a "fraction having substantially all proteins or peptides having a molecular weight greater than about 3 kDa and below the filtration limits of a normal kidney found in the biological fluid". This statement is not accurate. Page 42, lines 15-22 shows such a fraction. Furthermore, the data in Figure 2 supports the assertion that substantially all of the proteins present within the ranges listed would be present in such a claimed fraction. The claim language has been changes to match the specification language.

Claims 1, 3-19 and 25-38 were rejected under 35 USC 112, second paragraph, as being indefinite by reciting detecting at least one protein when the body of the claim does not refer to only one protein. The claim does not specify a numerical number of proteins to be detected because this number will vary depending on the original body fluid being used. If the initial sample contains only one protein within the claimed range in detectable amounts, then the final step of claim 1 will detect only that one protein. According, the claim is definite.

Claim 1 was also considered indefinite as to what is considered to be "low molecular weight proteins". The questionable language has been deleted but nonetheless was clear that low molecular weight proteins are those within the disclosed ranges. It will be appreciated that proteins are generally larger than the claimed about 3kDa limit and that many proteins have molecular weights well above the kidney filtration limit or the about 75kDa limit.

*Anderson et al.  
Serial No.: 09/921,004  
Page 8 of 12*

Therefore, reciting a protein mixture having range at the lowest end of protein sizes is appropriately called "low molecular weight proteins".

Claim 1 was considered vague and indefinite by reciting "substantially all" in part (b). This term is clear. It is well known that whenever handling any mixture of protein that a small amount may be lost during handling and the performance of the fractionation based on molecular weight step. From many locations in the specification, applicants wish to detect all proteins in the fraction by 2-DE using a single fraction having substantially all protein within a particular molecular weight range.

Claim 1 was also considered vague by the term "greater than about 3kDa". Page 42, first paragraph gives guidance to remove salts and metabolic byproducts (not proteins or their degraded peptides). Thus, the functional goal for the limit is given. Even if not so provided, the term is still definite on its face as a numerical value.

Claim 3 was noted to be indefinite by reciting "other fluid". This claim has been amended to clarify that this term qualifies a previous term.

Claim 7 was rejected as lacking antecedent basis for "said concentrating step". This language has been canceled.

Claim 31 was rejected as lacking a positive limitation to the term "capable of". The kidney is an organ and much more than a simple filter. This term is a positive limitation because some proteins are retained by the kidney by protein binding, absorption or by other means regardless of the protein's molecular weight. Such proteins or peptides are likely excluded from the set of those "capable of being filtered by a normal kidney". Therefore the term is a positive limitation and an indication of the protein mixture in the claimed composition.

Claim 36 is cited as having unclear language. This claim is canceled and the point moot.

Claim 38 is alleged to be vague and indefinite as to after which step does one perform the step of contacting the fluid with the antibody. In the specification examples, the

*Anderson et al.*  
*Serial No.: 09/921,004*  
*Page 9 of 12*

immunosubtraction step is performed after the molecular weight fractionation corresponding to between steps (c) and (d). However, it will be recognized that the step may be performed earlier between or with any steps after collection of the body fluid.

Claims 1, 3, 5, 10 and 19 were rejected under 35 USC 102(b) as being anticipated by Opiteck et al. The rejection contends that the reference fractionates proteins by size-exclusion chromatography followed by reversed-phase chromatography to separate the mixture into many protein fractions, which are later determined by mass spectrometry. This rejection is respectfully traversed.

At no point does Opiteck et al have a fraction with the characteristics claimed. Opiteck et al generates a large number of small fractions by molecular weight which are then individually subjected to reversed-phase chromatography. See page 353, column 2, lines 15-23. There is no separation of the first fraction as recited in the present claims. There is no recovery of the first fraction as recited in the present claims.

Furthermore, claim 1 recites detecting proteins or peptides from a body fluid. Opiteck et al's sample is from *E. coli*. A bacterium is not considered an animal and thus their sample not considered a "body fluid."

The last sentence of this rejection contains the assertion that the "recited claims do not exclude proteins having a molecular weight above the filtrations limits of a normal kidney being present in the first fraction." While the claims have been amended, they did include language exactly contrary to the examiner's assertion.

Claims 1, 3-5, 8, 9, 12-14, 17, 25, and 29-37 were rejected under 35 USC 103(a) as being unpatentable over Stevens in view of Liu et al. Stevens was cited to show removing interfering macromolecules from a sample before analyzing the proteins contained in it. Liu et al was cited as showing removing salts and other metabolites below 6kDa before analyzing the proteins in the sample. The examiner contends it would have been obvious to combine both techniques into a combined method. This rejection is respectfully traversed.

*Anderson et al.*  
*Serial No.: 09/921,004*  
*Page 10 of 12*

Stevens and Liu et al are treating different types of samples. Stevens is treating serum whereas Liu et al is treating urine. Indeed, Stevens provides a list of possible body fluids, which includes almost everything but urine. Even if such techniques could be combined, this is still not the present invention. Neither reference provides any suggestion to exclude proteins above an upper limit, for example, a protein having molecular weight of 200,000 daltons would be found in both Liu et al and Stevens. The present claims recite upper limits on the molecular weight of the proteins in the claimed fraction.

This exclusion of the highest molecular weight set of proteins is important to the present invention because in one embodiment the goal is to find plasma proteins filtered by the kidney, not those shed by the kidney, ureter, bladder, urethra, other urine contacting tissue or microbial protein.

Still further, neither reference discloses removing plural specific predetermined proteins by using an affinity column containing plural specific binding agents claimed in claim 29. This point is not directly addressed by the rejection.

Still further, the second fraction is not discussed by the references or any combination of references. Also, combining the first and second fraction is even less suggested by any combination of references.

Accordingly, no possible combination of these references suggests the claimed invention; therefore, the rejection should be withdrawn.

Claims 6 and 18 were rejected under 35 USC 103(a) as being unpatentable over Stevens in view of Liu et al and Furst et al. Stevens and Liu et al were applied as above. Furst et al is cited to show using density gradients and rate-zonal sedimentation and the rejection urges it obvious to combine this technique with the others.

Regardless, Furst et al does not compensate for the basic deficiency of Stevens and Liu et al. Furst et al adds nothing to suggest producing the claimed fraction or to add to the primary teachings to remove proteins having molecular weights above the claimed range. Accordingly, this rejection should be withdrawn.

*Anderson et al.*  
*Serial No.: 09/921,004*  
*Page 11 of 12*

Claim 7 was rejected under 35 USC 103(a) as being unpatentable over Stevens in view of Liu et al and O'Donnell et al. Stevens and Liu et al were applied as above. O'Donnell et al is cited to show adding protease inhibitors to urine to preserve the proteins. The examiner urges it obvious to combine this technique with the others.

After combining the O'Donnell technique, one does not teach the claimed invention or compensate for the basic deficiency of Stevens and Liu et al. Again, nothing suggests producing the claimed fraction or to remove proteins having molecular weights above the claimed range. Accordingly, this rejection should be withdrawn.

Claims 10, 11 and 19 were rejected under 35 USC 103(a) as being unpatentable over Stevens in view of Liu et al and Opiteck et al. Opiteck et al was cited to show using reversed-phase liquid chromatography and mass spectrometry to analyze the protein samples. The rejection urges it obvious to use these techniques with the basic sample preparation techniques of Stevens and Liu et al. This rejection is respectfully traversed.

Even combined in such a manner, the combination of references does not show preparing a fraction with substantially all proteins from a body fluid within the range claimed. There is no suggestion to remove the proteins having a molecular weight above the range claimed. Accordingly, when Opiteck et al is applied as above, it adds nothing to compensate for this deficiency. Therefore, this rejection should be withdrawn.

Claims 15, 16 and 27 were rejected under 35 USC 103(a) as being unpatentable over Stevens in view of Liu et al and Hage et al. Hage et al was cited to show using affinity chromatography to selectively bind almost any protein. From this the rejection urges it obvious to use this technique in the Stevens method with the basic sample preparation techniques of Stevens and Liu et al. This rejection is respectfully traversed.

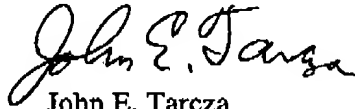
Even combined in such a manner, the combination of references does not show preparing a fraction with substantially all proteins from a body fluid within the range claimed. There is no suggestion to remove the proteins having a molecular weight above the range claimed. Accordingly, when Hage et al is applied as above, it adds nothing to compensate for this deficiency. Therefore, this rejection should be withdrawn.

*Anderson et al.  
Serial No.: 09/921,004  
Page 12 of 12*

In view of the above amendments and comments, the claims are now in conditions for allowance and applicants request a timely Notice of Allowance be issued in this application. If any issues or questions remain, the examiner is encouraged to call the undersigned at the telephone number below.

The commissioner hereby is authorized to charge payment of any fees under 37 CFR § 1.17, which may become due in connection with the instant application or credit any overpayment to Deposit Account No.500933.

Respectfully submitted,



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